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Restoring an ISO:5840-compliant Pulse Duplicator Device for Hydrodynamic Performance Characterization of Artificial Cardiac Valves

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Abstract

During the summer of 2021, I was employed as an intern at Dynatek Labs, an implantable prosthetics testing company located in southern Missouri. My primary project was to modernize an abandoned pulse duplicator device and protocol to allow the company to re-enter a market area which they left nearly 15 years prior: heart valve testing. The company halted this initiative due to changes in international testing standards in previous years. The International Standards Organization Cardiac Valves Working Group released the latest version of standards concerning artificial heart valve testing (ISO 5840) in January of 2021. Accordingly, my project required that I become abundantly familiar with requirements for the apparatus, procedure, and testing conditions for *in vitro* evaluations of artificial heart valves. With this knowledge, I made appropriate alterations to the existing device, software, and operation protocols to bring them into accordance with updated regulatory demands. Additionally, I coordinated the purchase of a new particle image velocimetry system which would be used to further characterize implants' thrombogenic and haemolytic potential. I generated new documentation for the device including a comprehensive manual, user guide and test protocol. Hundreds of tests were performed to fully calibrate, produce the documentation, and implement the new system and device software. By the conclusion of my appointment at Dynatek Labs, the pulse duplicator was fully functional, data acquisition was conducted in full accordance with the most recent standards, and the auxiliary PIV system was successfully integrated into the overall device setup.

Introduction

Dynatek Labs is a medical device testing and test equipment manufacturing company located in Galena, MO, which specializes in the testing of cardiovascular prostheses, particularly stents. In the late 1990's, the company was an industry leader in the testing of artificial heart valves,

which was performed using one of Dynatek's novel testing devices: the MP3 pulse duplicator. This then-novel device is not only capable of recreating realistic pressure profiles across valves in both aortic and mitral positions, but also provides full visual access to both ends of each valve. The MP3 also utilizes a compliant arterial chamber to mimic the flow and pressure response of systemic vasculature, making it the first pulse duplicator of its kind. Unfortunately, a lack of market interest resulted in suspension of the project in or around 2008. The device and testing protocol laid dormant for over a decade, and the then-latest hardware and software configurations were never used to perform a commercial test.

The International Standards Organization (ISO) Cardiac Valves Working Group is an international body responsible for creating and regulating apparatus and testing requirements for cardiac valve prostheses. Dynatek's ownership regularly takes part in the crafting of the standards published by this regulatory body. In January 2021, the group published documents outlining new testing requirements and standards for cardiac valves. These standards are known generally as ISO 5840. In response to these discussions and new standards, Dynatek management sought to reenter the marketspace of cardiac valve testing. After an initial market analysis, it was estimated that the company could increase annual sales by over $1 million by offering cardiac valve testing.

Pulse Duplicators and the MP3

A pulse duplicator device is an essential tool to evaluate the performance of artificial heart valves. The purpose of this device is to accurately recreate the intense oscillating pressure conditions present in the heart, arguably the most mechanically harsh environment of our viscus organs. A pulse duplicator accomplishes this purpose by pumping fluid, typically distilled water modified with specific salts and antimicrobial chemicals, through a series of tubes and chambers

which functionally resemble a human heart. A cardiac valve is installed or implanted at a position within the device that is analogous to the valve's function inside the body. A simplified schematic representation of the common components for constructing such a device can be seen here as Figure 1.

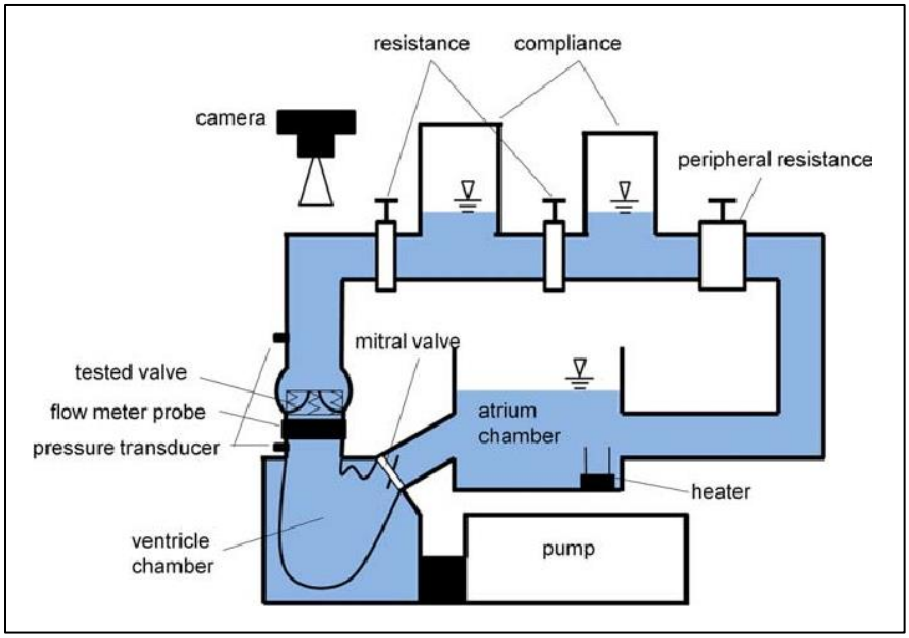

Figure 1 – Schematic representation of basic components in a standard pulse duplicator. Feng et al. (2017).

A wide variety of hydrodynamic conditions can be found in the human heart. These conditions, which include heart rate, cardiac output, systolic duration, and transvalvular pressure, can vary across time and between individuals. To accurately simulate these varying conditions, it is important to carefully consider multiple aspects of pulse duplicator device design. Some pulse duplicators accommodate the testing of valves designed for only a single valve position (i.e. aortic valves), while other designs allow for placement of two valves. When two valves are

present, these most often represent the valves of the left heart, where pressure differences are normally much higher[2,3]. The ventricular pumping action of a pulse duplicator can be provided either by a pneumatic pump or a piston actuator[3]. Simulation of vascular compliance can also vary widely between pulse duplicator designs: some systems are rigid, while others may have a series of flexible tubes, compliant chambers, and chokepoints[3]. By carefully selecting appropriate design elements and tuning the device's parameters, it is possible to simulate a range of physiological conditions.

The MP3 pulse duplicator, shown in Figure 2, was originally designed by Dr. Milt Swanson in the early 1980's at Washington University. The pumping action of the MP3 is performed by a piston-actuator drive assembly. Various improvements and total redesigns have been performed over the years. The original independent controller has been replaced by a controller/PC combination with automated real-time data visualization, processing, and recording, as well as advanced and precise control of actuator motion. The vascular loop is made from compliant tubing and was quite a novel improvement at the time of the MP3's development, as it allowed for far more realistic simulated back pressure on aortic valves. Tubing clamps are used throughout the length of the loop to mimic vascular resistance. The systemic reservoir holds the bulk of the working fluid, while the mitral assembly holds a smaller reserve to allow for more favorable conditions as fluid enters the rigid ventricle assembly. As the drive assembly retracts the piston in the pump assembly, fluid is pulled in from the mitral assembly through the mitral valve. The drive then performs a forward stroke, ejecting test fluid from the ventricle assembly, through the aortic valve, and into the vascular loop. The pressurized fluid then flows through the sectioned compliant chambers and resistance clamps back into the systemic reservoir, where pressure is atmospheric.

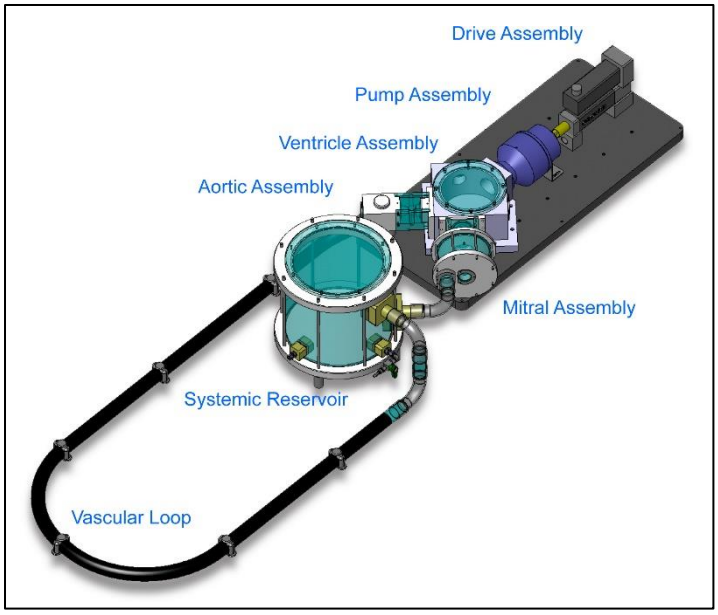

Figure 2 – Diagram of the MP3 pulse duplicator. In this view, fluid flows in a counterclockwise direction from the systemic reservoir to the ventricle assembly and through the vascular loop.

ISO 5840:2021

The ISO 5840 standard (ISO 5840:2021 Cardiovascular implants - Cardiac valve prosthesis) is, at the time of writing, the current regulatory authority on *in vitro* assessment of artificial cardiac valves. The first version of the standard was published in 1984; thus, the current edition represents nearly four decades of accumulated knowledge and has expanded its scope to accommodate newly invented styles of cardiac valves[4]. Split into three volumes, this international standard provides over 200 pages of definitions, diagrams, and testing guidelines to ensure *in vivo* suitability of cardiac prosthesis. The previous revision of ISO 5840 was published in 2015; therefore, the ISO 5840:2021 standards represent over 5 years of additional field-specific knowledge and considerations[4]. Regulations cover both transcatheter and surgically implanted heart valves, ranging over a wide variety of topics such as material testing, apparatus and fixture guidelines, reporting requirements, and packaging. Guidelines are also

provided for more specific tests such as evaluating paravalvular leakage, transcatheter implantation into existing prostheses, and implantation in scenarios of trileaflet calcific stenosis[2,4].

Several important considerations were added in this most recent version. Prominent among those is the inclusion of a new annex, entitled “Assessment of Implant Thrombogenic and Haemolytic Potential.” Thrombogenic potential is defined as the ability of a device to generate blood clotting and/or thrombus when in contact with the blood. Haemolytic potential is defined as the ability of a device to cause rupturing (lysis) of red blood cells (erythrocytes). This annex outlines three methods of measuring thrombogenic and haemolytic potential of heart valves, including computational fluid dynamics (CFD), blood loops, and particle image velocimetry (PIV)[2].

CFD is a method of assessing haemolytic potential which simulates fluid flow through a 3-dimensional *in silico* device model. Specifically, the method seeks to identify potential areas of high shear stress caused by elements of the device model’s geometry. Blood loops are an *ex vivo* method of assessing thrombogenic potential; human and/or animal blood is used as the test medium, and later analyzed for thrombus formation and haemolysis[4].

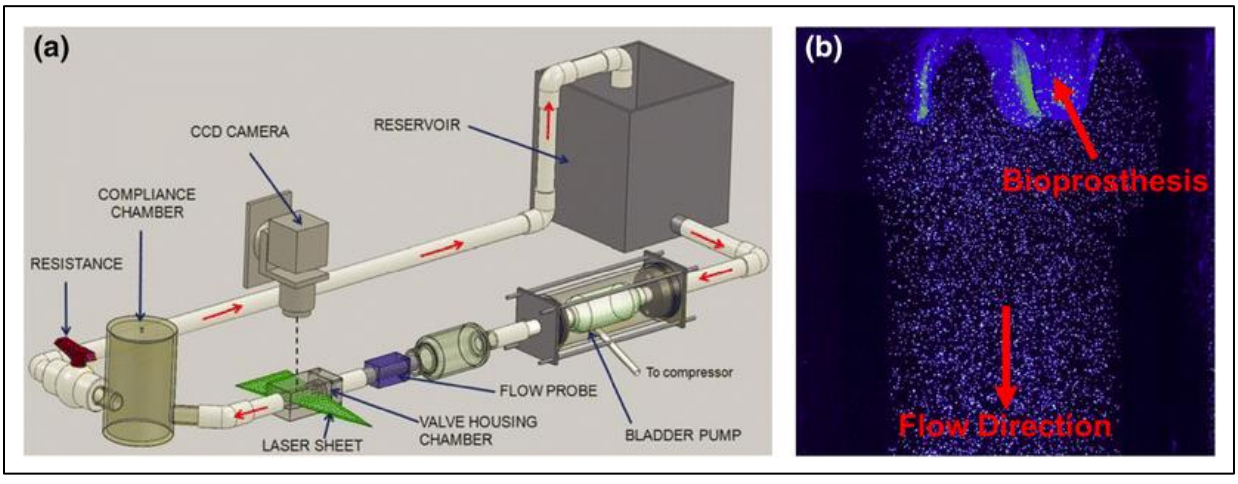

Figure 3 – (a) Schematic depiction of a typical single valve pulse duplicator device with laser sheet and camera for PIV data acquisition. (b) Example pre-processed image captured by PIV system. Raghav, Sastry, & Saikrishnan (2018).

Particle image velocimetry, or PIV, is an *in vitro* method of visualizing flow and predicting both thrombogenic and haemolytic potential. Typically, a PIV system consists of at least one highspeed camera, a high-powered laser with light sheet optics, and a synchronizing controller (See Fig. 3.a). When used together with a pulse duplicator, a full PIV system can determine the shear stresses and areas of fluid stagnation that occur within the geometry of a cardiac valve[2,5]. High shear stress and fluid stagnation are highly correlated with haemolysis and thrombosis formation, respectively[2].

The pulse duplicator test medium used during PIV assessment requires two additional components to provide meaningful results. Firstly, the medium must be mixed with glycerin; the purpose of this is twofold. Glycerin alters the viscosity of the medium to mimic that of human blood, a crucial step given that shear stress is a function of viscosity. Furthermore, glycerin alters the refractive index of the medium. PIV testing is a visual assessment, and visual clarity and elimination of optical distortion are highly important. By carefully matching the refractive index of the medium to the refractive index of the transparent valve assembly, optical integrity is maintained, and quality image data can be acquired (See Fig. 4). Secondly, the test medium must be seeded with either reflective or fluorescent seeding particles, which are typically around 10 microns in diameter. During PIV, high-powered laser light interacts with these particles, making them clearly visible to the highspeed camera.

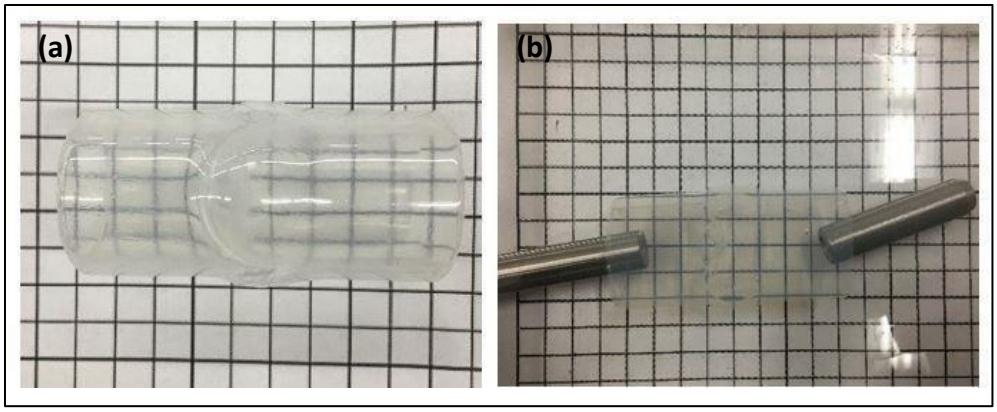

Figure 4 – Example of a light refraction in a silicone aortic valve model before (a) and after (b) refractive index matching using a 40%-60% water-glycerin solution. Zhang & Zhang (2018).

The high-powered (typically Nd:YAG) laser creates a beam, which is then split into a laser sheet by an optical light sheet generator[5,6]. This laser sheet travels through the enhanced medium to illuminate a plane of seeding particles surrounding the valve. The camera is installed such that the image frame is parallel to the laser sheet. The controller synchronizes the laser flash and image capture. Images are reported to an image processing software. Particle movements between consecutive images are tracked and used to calculate local fluid velocities surrounding the valve. Depending on the setup and number of cameras, these velocities may be detected in two or three dimensions. By inputting the parameters of the test medium, it is further possible to visualize the shear stress at any point within the image plane, and subsequently identify any problematic elements of a valve's design.

Due to the length of time that the MP3 was out of commission, an ISO 5840-compliant device restoration would also need to meet requirements introduced in previous versions of these standards. Specifically lacking from the MP3 were three new reporting requirements: mean back pressure, regurgitant fraction (RF), and effective orifice area (EOA). These values can be calculated from basic pressure and flow measurements bounded by specific timepoints in a

typical cardiac cycle (See Fig. 5). In addition to the reporting requirement, both RF and EOA are asserted as primary acceptance criteria for the suitability of any cardiac valve[2]. ISO 5840 defines RF as the regurgitant volume of the valve expressed as a percentage of the forward flow volume[2]. EOA is further defined as the valve orifice area which has been derived indirectly from flow and pressure or velocity data[2].

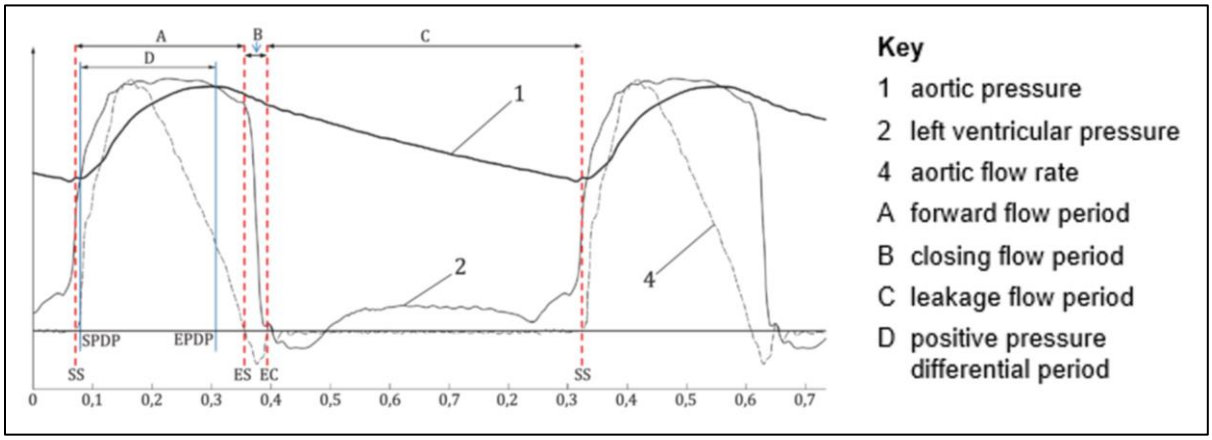

Figure 5 – Example target waveform of cardiac pressure and flow measured at the aortic valve in a pulse duplicator, as suggested by the ISO 5840 standard. Basic waveforms and time indicators like these are used to calculate important valve acceptance criteria such as RF and EOA. International Organization for Standardization (2021).

The following standardized equation is used to determine effective orifice area:

$$A_{eo} = \frac{\sqrt{\frac{\int_{t_1}^{t_2} q_v(t)^2 dt}{t_2 - t_1}}}{51.6 \times \sqrt{\frac{\Delta p}{\rho}}}$$

Equation 1

where A_{eo} is the effective orifice area (cm^2); q_v is the instantaneous flow rate at time (t); t_1 and t_2 are the times at the start and end of the positive differential pressure period, respectively (See Fig. 5); Δp is the mean pressure difference (measured during the positive differential pressure period) (mmHg); and ρ is the density of the test fluid $(g/cm^3)^2$. This derived area allows for relatively balanced comparisons between valves of drastically different designs. Definitions for RF and mean back pressure values are much simpler; further details can be found in the publicly available definitions section of ISO 5840.

Implementation of Device Requirements into Software

As indicated above, the MP3 software needed an update to accommodate the new reporting requirements. The latest MP3 software had been written using National Instruments™ (NI) LabVIEW, a graphical scientific programming language which uses a visual block diagram interface rather than a typical, text-based development environment. Variables are passed through a network of node-connected blocks, demonstrated below in Figure 6. This versatile programming language is quite useful in cases where a device-specific controller is required to communicate and transfer data to a nearby computer, as LabVIEW can run on both a standard computer processor and a NI reconfigurable I/O (RIO) board.

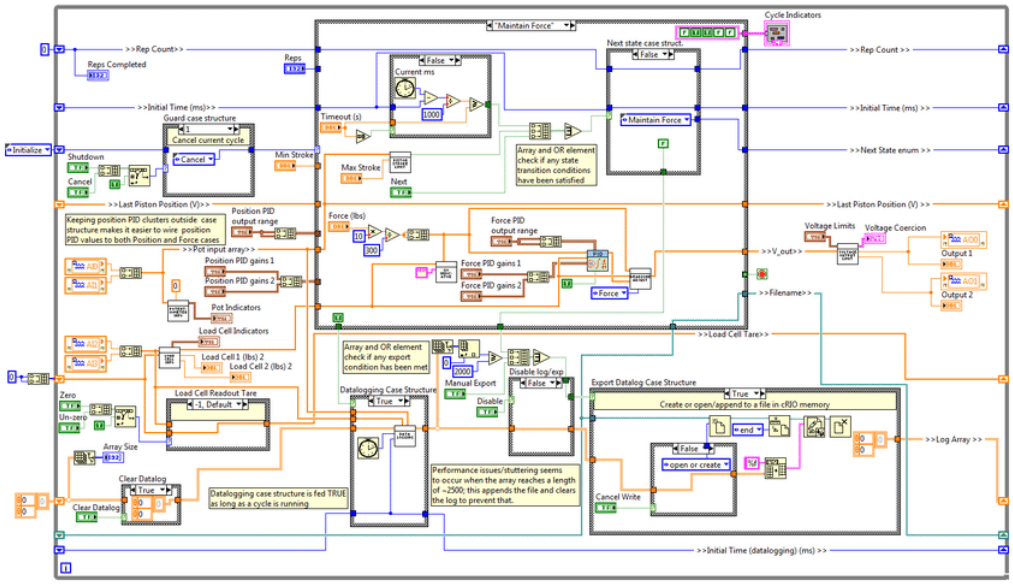

Figure 6 – Publicly shared example of National Instruments™ LabVIEW Block Diagram. Syed & Seipel (2015).

Aside from the technical requirements listed above, other software concerns and feature requests were documented. All software requests were presented to the original developer of Dynatek's MP3 software, who then made a number of appropriate changes to the software. Required alterations included the addition of a feature allowing simultaneous calibration of all pressure transducers, updates to controller alarm features, and added functionality to calculate and save the new reporting requirements. Unfortunately, due to constraints on the developer's time, not all features were fully implemented, and those that were could not be fully tested. It thereafter became expedient that I learn the LabVIEW programming language and implement the remaining functionalities to the software. These tasks included a considerable amount of training to learn the LabVIEW language, which I then used to modify the MP3 software to accommodate the remainder of these requirements and other productivity tools. Among these other tools was a simplified interpretation of real-time temperature measurements, improved and more relevant method of inputting testing volume parameters, and further implementation of

the new pressure calibration interface. All required metrics and suggested improvements were implemented into the MP3 software package. Appropriate additions were made to the MP3 manual to reflect changes in the software UI and functionality.

Developing New MP3 Usage Guidelines

During the time when the MP3 was not in use for commercial tests, it was periodically taken from storage for experimental and evaluation purposes. Despite this, much of the knowledge regarding how to properly set up and perform a test using the device had been lost to time. Thus, it became necessary that I spend considerable quantities of time reading previous manuals and performing mock tests to rediscover this knowledge. The latest in-depth documentation on how to perform tests with the MP3 came from a manual created many years previously when the device was run solely by an independent controller (no PC interface). It was my intention to find the best practices for performing hydrodynamic performance testing such that I would be capable of documenting these practices in detail and thoroughly teaching them to other technicians. After I read the manuals, it was clear that there were many factors to consider when attempting to tune the pressure waveforms produced by the MP3 to resemble those provided within the ISO 5840 standards (Fig. 5). The primary and most complex factor was the relationship between the size of a compliant chamber, the simulated resistance through the chamber, and the behavior of the pressure waveform at differing timepoints within the cardiac cycle. A second factor was the compliance of the ventricular chamber itself.

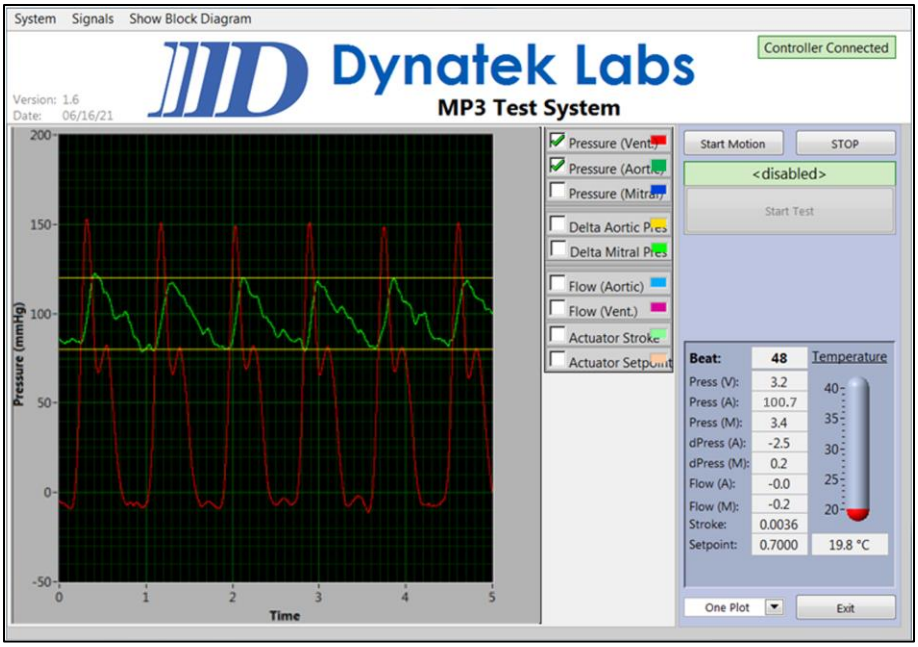

Figure 7 – User interface of MP3 software with test running at nominal conditions (70 bpm, 5 lpm, 35% systolic duration, 120/80 mmHg). The green and red lines represent aortic and ventricular pressures, respectively.

When testing hydrodynamic performance, it is required to evaluate cardiac valves across a range of physiological conditions. The nominal conditions asserted by ISO 5840 are 70 bpm heartrate, 5 liters per minute cardiac output, 35% systolic duration, and a pressure range of 120/80 mmHg[2]. Many of the necessary tests required for valve performance characterization are conducted at these conditions. However, some characterizations must also be performed at conditions of both hyper- and hypotension and at extreme heartrates and cardiac outputs[2]. For this reason, it was not only necessary to understand how to configure the device for a nominal heart waveform, but also how changes in each configurable element affected the waveform output. With little guidance outside of technical manuals, these relationships were rediscovered over several weeks of testing and pattern recognition. Once enough information was gathered, documentation and a user guide were created to outline the proper tuning process. Additionally,

four technicians and engineers were trained on how to tune the MP3 and navigate the software sufficiently to perform a hydrodynamic performance assessment.

Research and Implementation of PIV System

As outlined above, one of the most prominent changes in ISO 5840:2021 is the required assessment of thrombogenic and haemolytic potential. Of the three methods introduced, PIV was most relevant to the capabilities and interests of Dynatek Labs. With a functioning pulse duplicator, Dynatek needed only to acquire a PIV system to perform these evaluations. It became my task to orchestrate Dynatek's purchase and implementation of a new PIV system. After an initial market research on PIV system providers, the search was narrowed to three companies which offered product systems that would adequately meet our needs. Sales representatives from each of these companies were contacted both by email and telephone. Details on each system and provider were compiled and compared. Primary factors included pricing, ability to upgrade or expand the system, availability of technical support, maturity of the included image processing software package, delivery time, and past exposure or experience of the company with cardiac valve testing. After comparing and discussing the options with senior company officials, a decision was finalized, and the purchasing process began.

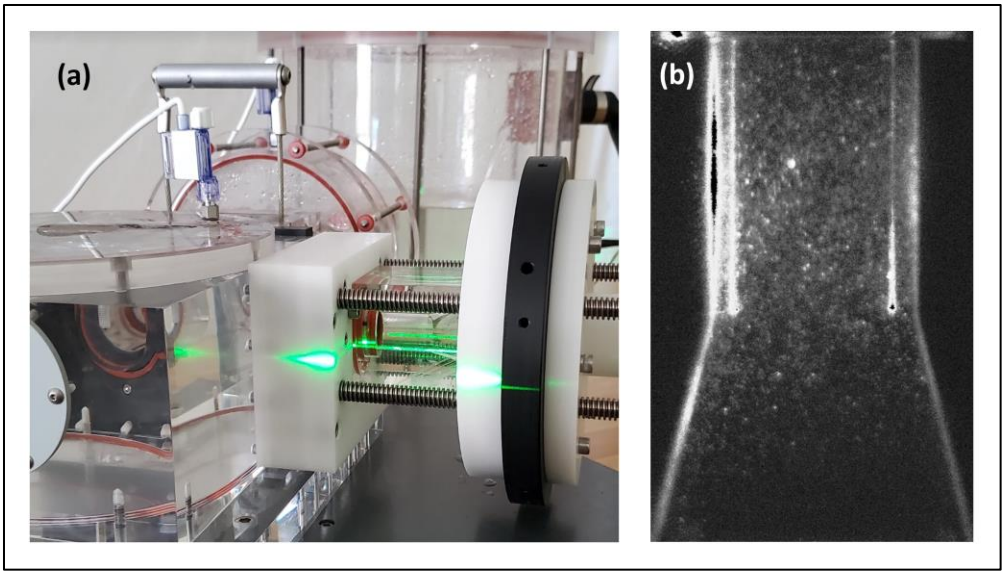

Figure 8 – (a) MP3 pulse duplicator during a cardiac valve PIV test. The green laser sheet passes through the fluid immediately downstream of the valve in testing. (b) PIV image generated on the MP3 setup. Images can be processed to calculate local shear stresses.

Once the PIV system was delivered, it underwent an extensive setup process. Proper implementation of the system onto the MP3 required high visual access from multiple angles in the region where the cardiac valve would be mounted. Although the MP3's existing aortic assembly allowed easy visual access from both ends of the valve, this access was not available from the sides, which would be necessary for proper laser illumination and high-speed imaging of the entire valve region. Dynatek's lead mechanical engineer was tasked with designing a new aortic assembly which could accommodate these requirements. The assembly was designed and manufactured, allowing for further implementation of the system. The camera, laser, synchronizer, and various controllers were mounted or installed as necessary. The controller software and image processing package were also installed. Through close coordination with an engineer from the PIV system provider, hardware elements were installed, software parameters were set, and PIV images were captured (See Fig. 8). Images were then processed to provide

advanced insights into the fluid behavior within and surrounding the valve. Metrics available for visualization include average and instantaneous velocity, fluid vorticity, and shear stress.

Conclusion

The updated ISO 5840:2021 standards prompted Dynatek Labs to reconsider the field of cardiac valve testing. With the addition of new testing requirements and assessment methods, an opportunity opened itself for Dynatek to revamp the software and data acquisition accessories of the MP3 pulse duplicator. To realize this potential, it was first necessary to become familiar with the new requirements for assessing hydrodynamic performance of heart valves by studying the updated standards. Once the new device requirements were clearly defined, appropriate software adjustments were implemented to allow for calculation of reporting important metrics such as effective orifice area. Considerable time was spent redocumenting best practices for recreating realistic cardiac pressure conditions within the device. Multiple training sessions were carried out to instruct these methods to other company employees. Additional measures were taken to characterize the thrombogenic and haemolytic potential of a valve. A PIV system was selected for purchase and installed, and a new aortic valve assembly was designed to allow for multidirectional valve visibility. As a result of these combined efforts, employees at Dynatek are now trained to use the MP3 pulse duplicator, which now provides up-to-date reporting metrics, and is further equipped with a PIV for advanced hydrodynamic assessments.

However, there are still improvements which can be made on this project. Although many advancements were made to the MP3 software, the recorded test data is not encrypted, and therefore does not meet requirements for ISO/IEC 17025 – general requirements for the competence of testing and calibration laboratories. Following this adjustment, the software

would need to undergo a revalidation process. Furthermore, the PIV system has a built-in functionality for image synchronization; this could be developed into a feature which extracts velocity and shear stress data from specific timepoints within the cardiac cycle, which feature is suggested in the ISO 5840 standard[2]. And although the MP3's design makes it highly configurable and excellent for conducting a wide range of in-house tests, its particularly bulky layout and complexity of tuning make it unfeasible to sell as a commercial product. Generally, a more compact and specific product would have a better chance at outcompeting competition, if Dynatek were to choose to take the device in this direction. Nevertheless, the improved MP3 system today stands to provide meaningful and novel technological contributions to the market and research field of artificial heart valves.

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